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Date of Deposit: February 25, 2004

Attorney Docket No. 19705-010

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT(S):	Thomas T. Andersen *et al.*		
APPLICATION NO:	09/872,623	EXAMINER:	Sheela Jitendra Huff
FILING DATE:	June 2, 2001	ART UNIT:	1642
FOR:	*ALPHA-FETOPROTEIN PEPTIDES AND USES THEREOF*		

MAIL STOP AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF PRIOR INVENTION UNDER 37 C.F.R. §1.131

We, Thomas T. Andersen, James A. Bennett, Herbert I. Jacobson, and Fassil B. Mesfin, hereby declare and state as follows:

1. We invented the inventions described in the Application, and reduced to practice in the United States at least the inventions described in claims 1-3, and 5.

2. We are aware that in the final Office Action mailed August 25, 2003 (Paper No. 16) in the above-identified application ("the Application"), the Examiner has rejected claims 1-3, and 5 under 35 U.S.C. § 102(a) as being anticipated by Mesfin *et al.*, Proc. of the American Assn. for Cancer Research, 42:778 (2001) ("Mesfin"). We are also aware that, according to the Examiner's Advisory Action, mailed December 30, 2003, this is the sole remaining rejection for this application. It is our understanding that Mesfin has been cited by the Examiner because it discloses sequences within the scope of claims 1-3, and 5, namely EMTOVNOG (SEQ ID NO:4) and EMTOVNOGQ (SEQ ID NO:5). We now submit this Declaration to establish that the Mesfin publication does not describe an invention that was known or used, before invention of claims 1-3, and 5 by Applicants, under 35 U.S.C. § 102(a). A copy of the pending claims, as amended in our Amendment and Response filed on November 25, 2003, is attached hereto as Exhibit A.

3. Reduction to practice (completion) of the invention described and claimed in at least amended claims 1-3, and 5 of the Application is demonstrated by the documents attached hereto as Exhibit B. Mesfin was contributed and published for the 92nd Annual Meeting of the American Association for Cancer Research, which occurred on March 24-28, 2001. A copy of the Mesfin Abstract, and of the AACR's web page lisitng the dates for the 92nd Annual Meeting, are attached hereto as Exhibit C.

4. Presented in Exhibit B are six (6) pages which are true copies from Applicants' notebooks leading to the invention of claims 1-3, and 5. These pages show the synthesis and bioassay of SEQ ID NO:5 (EMTOVNOGQ) on June 3-4, 2000, and June 8-9, 2000, respectively. As denoted in our lab notebooks, the name of the peptide is 9merHyPro. This is shorthand for a peptide of 9 amino acids wherein the proline (P) residues were both substituted by Hydroxyproline (O). Although the sequence on the first sheet indicates Pro in positions 4 and 7, the synthesizer computer uses the Pro code by default. The synthesizer was not re-programmed to print HyPro in place of Pro.

5. Page 2 of Exhibit B is dated June 8, 2000 and represents the concentrations of the peptide to be tested in the Uterine Growth Assay as disclosed in the instant application. The remaining pages of Exhibit B, dated June 9, 2000, detail the findings of the assay (*e.g.*, antiestrotrophic activity of EMTOVNOG (SEQ ID NO:4) and EMTOVNOGQ (SEQ ID NO:5)).

6. Thus, peptides disclosed by Mesfin (EMTOVNOG (SEQ ID NO:4) and EMTOVNOGQ (SEQ ID NO:5)) are documented to be in our possession nearly one year before the March 2001 publication date of Mesfin. Accordingly, Mesfin is not prior art under 35 U.S.C. § 102(a) and cannot anticipate claims 1-3, and 5. Therefore, we respectfully submit that the rejection should be withdrawn.

7. We further declare that all statements made herein of our own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001 and that willful

false statements may jeopardize the validity of this application and any patent issuing therefrom.

Thomas T. Andersen

Signed at Albany, NY

this 24 day of February, 2004

James A. Bennett

Signed at Albany NY

this 24th day of February, 2004

Herbert I. Jacobson

Signed at Albany, NY

this 24th day of February, 2004

Fassil B. Mesfin

Signed at Albany, NY

this 24th day of February, 2004

PENDING CLAIMS

Attorney Docket No.:	19705-010	**Examiner:**	Sheela J Huff
U.S.A.N.:	09/872,623	**Art Unit:**	1642
Applicants:	Andersen et al.	**Phone No.:**	(703) 305-7866
Filing Date:	June 2, 2001	**Attorney/TS**	IRE/NSB/CEB
Assignee:	MTAP		
Title:	*Alpha-Fetoprotein Peptides and Uses Thereof*		
Pending Claims:	Claims following the Response to Final Office Action, mailed 8/25/03		

1. A peptide which is derived from the alpha-fetoprotein having SEQ ID NO:6, wherein said peptide has antiestrotrophic activity and is eight to twenty amino acids long.

2. The peptide of claim 1, wherein said peptide is linear.

3. The peptide of claim 1, wherein said peptide is cyclic.

4. The peptide of claim 1, wherein one or more of said amino acids is a (D)-amino acid.

5. The peptide of claim 1, wherein the amino acid sequence of said polypeptide is selected from the group consisting of:

SEQ ID NO:4:	EMTOVNOG
SEQ ID NO:5:	EMTOVNOGQ
SEQ ID NO:8:	EMTOVNPG
SEQ ID NO:9:	EMTOVNPGQ
SEQ ID NO:10:	EMTPVNOG and
SEQ ID NO:11:	EMTPVNOGQ,

or a peptidomimetic of said peptide.

6. The peptide of claim 1 labeled with a detectable marker.

7. The peptide of claim 6 wherein the detectable marker is a radiolabel.

8. The peptide of claim 7 wherein the radiolabel is a radiolabeled additional amino acid.

9. (Allowed) A dimeric peptide consisting of two peptides of eight to twenty amino acids in length which comprises a hydrophilic analog of an alpha-fetoprotein peptide having SEQ ID NO:6: EMTPVNPG.

10. (Allowed) The dimeric peptide of claim 9 wherein the two said peptides are SEQ ID NO:4 and SEQ ID NO:5.

11. (Allowed) The dimeric peptide of claim 10 wherein the two said peptides are SEQ ID NO:3 and SEQ ID NO:10.

12. (Allowed) A multimeric peptide consisting of three or more peptides of claim 1.

13-15. Canceled

16-22. Withdrawn.

Notebook Name:	9merHyPro
Protocol Name:	\Template
Chemistry Name:	\OH Derivatives
Final Cycle:	Fmoc Off
Start time:	06/03/00, 02:09:11 PM
Finish time:	06/04/00, 01:38:41 AM
Status:	Complete
Instrument name:	Pioneer
Synthesis Position:	1
Sequence Name:	9merHyPro
Sequence:	Glu - Met - Thr - Pro - Val - Asn - Pro - Gly - Gln -
Sequence length:	9
First AA Support:	Off

Uterine Bioassay
6-8-00

I	Sal		Sal
II	Sal		E_2
III	Fresh 9mer oH-trol made 6-4-00 thawed 6-6-00	1mg	E_2
IV	"	10 mg	E_2
V	"	100 mg	E_2
VI	"	1 ug	E_2
VII	"	10 ug	E_2
VIII	"	100 ug	E_2

weigh out 700 ug dissolve in 3.5 ml. PBS 200 ug/ml in 0.1

0.3	+ 2.7	20 ug/ml
"	"	2 ug/ml
"	"	200 ng/ml
"	"	20 ng/ml
"	"	2 ng/ml

Neonatal Autopsy

Date 06-9-00

Treatment:	Birth Date	Age in Days	Body wt. (grams)	Uterine wt. (mg)	UW/BW ratio ($\times 10^{-3}$)	$\bar{X} \pm SD$
I sal. sal						
1			7.94	4.9	0.61_7	$0.83_5 \pm 0.16_8$
2			8.34	8.4 JB	1.00_7	
3			8.30	6.8 JB	0.81_9	
4			8.12	8.0	0.98_5	
5			7.35	5.6 JB	0.76_2	
II sal E_2						
1			9.96	15.0 JB	1.67_4	$1.61_2 \pm 0.16_0$
2			7.61	12.2	1.60_7	
3			8.25	13.6 JB	1.64_8	$\bar{S}_{\bar{X}} = 0.77_4$
4			8.35	14.9 JB	1.78_4	
5			7.69	10.4	1.35_2	

1.41$_2$/0.83$_5$

Neonatal Autopsy

Date 06-9-00

Treatment:	Birth Date	Age in Days	Body wt. (grams)	Uterine wt. (mg)	UW/BW ratio ($\times 10^{-3}$)	$\bar{X} \pm SD$
~~VII~~ Fresh 9mist E_2						
III Hy-pro 1			9.14	9.0 JB	0.984	$1.61_1 \pm 0.41_5$
~~10 ng~~ Yng 2			7.66	11.3	1.47_5	
3			8.69	14.5 JB	1.66_8	—
4			7.40	15.4 JB	2.08_1	
5			8.67	16.0	1.84_6	
IV ~~VIII~~ Fresh 9mist E_2						
Hy-pro 1			8.60	13.5 JB	1.57_0	$1.48_5 \pm 0.14_4$
~~100 ng~~ 2			8.90	10.9	1.22_5	
10 ng 3			7.35	11.5 JB	1.56_4	0.12_4 15%
4			8.38	13.1 JB	1.56_3	
5			7.44	11.3	1.51_9	

1.61₂ / 0.83₉

Neonatal Autopsy

Date 06-8-00

Treatment:	Birth Date	Age in Days	Body Wt. (grams)	Uterine Wt. (mg)	UW/BW ratio ($\times 10^{-3}$)	$\bar{x} \pm SD$
V Fresh Suer E_2						
Hy-pro 1			8.76	12.6 JB	1.43₈	$1.48_1 \pm 0.08_5$
100 ng 2			8.68	13-9 JB	1.60₁	
3			7.80	11.8	1.51₃	0.13_1 16%
4			7.98	11-8 JB	1.47₉	
5			8.16	11.2 JB	1.37₂	
VI Fresh Suer E_2						
Hy-pro 1			8.68	12.2	1.40₆	$1.40_4 \pm 0.13_6$
1 ug 2			7.38	9-8 JB	1.32₈	
3			7.92	9.8 JB	1.23₇	0.20_3 24%
4			8.08	12.8	1.58₄	
5			8.58	12.8 JB	1.49₂	

1.61₂ / 0.83₈

Neonatal Autopsy

P4

Date 06-9-00

Treatment:	Birth Date	Age in Days	Body wt. (grams)	Uterine wt. (mg)	UW/BW ratio ($\times 10^{-3}$)	$\bar{X} \pm SD$
VII Fresh Prep E_2						
Hy-pro 1			7.76	11.1 JB	1.43_0	$1.44_1 \pm 0.15_5$
10 µg 2			7.93	10.1	1.27_4	
3			9.01	14.5 JB	1.60_9	0.17_1 20%
4			8.72	13.9	1.59_4	
5			8.23	10.7 JB	1.30_0	
VIII Fresh Prep E_2						
Hy-pro 1			8.02	14.2 JB	1.77_1	$1.76_2 \pm 0.39_0$
100 µg 2			8.01	10.9	1.36_1	
3			7.87	14.0 JB	1.77_9	—
4			8.56	20.4 JB	2.38_3	
5			8.51	12.9	1.51_5	

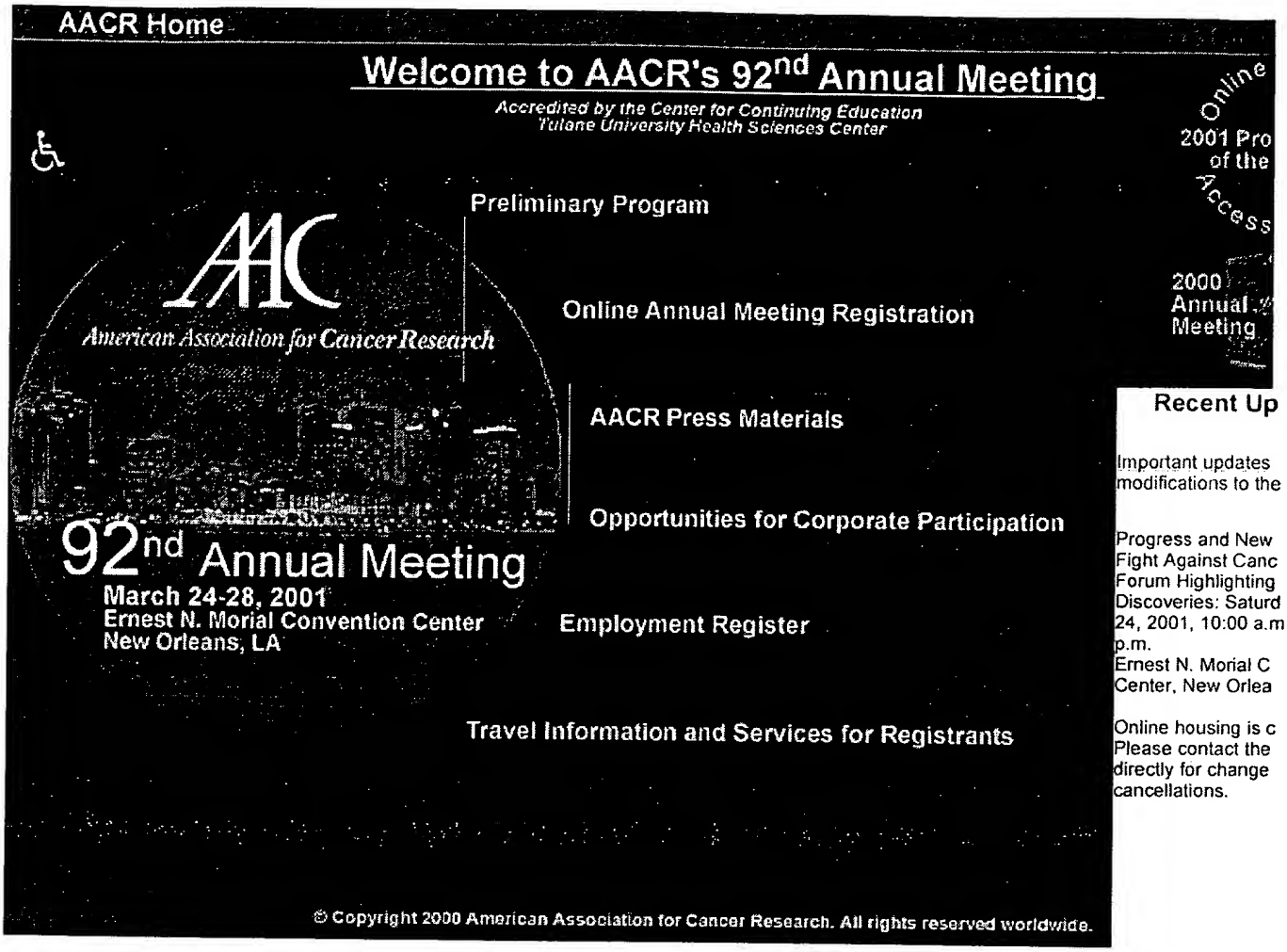
American Association for Cancer Research
The 92nd Annual Meeting

Novel Analogs of an Anti-Breast Cancer Octapeptide

F.B. Mesfin, J.A. Bennett, S.J. Zhu, H.I. Jacobson, T.T. Andersen
Albany Medical College, Albany, New York 12208

An anti-estrogenic octapeptide (sequence EMTPVNPG) derived from alpha-fetoprotein inhibited estrogen-stimulated growth of immature mouse uterus and estrogen-dependent proliferation of T47D human breast cancer cells in culture. However, these biological activities diminished as a function of time in storage even in the lyophilized state. Mass spectroscopy analysis indicated no chemical modifications of the peptide during storage, suggesting that chemical modifications were not the cause of diminished biological activity. Gel-filtration chromatography of stored peptide yielded a high molecular weight fraction that was biologically inactive, but incubation of this fraction with 4M urea prior to bioassay restored the activity. These results suggest that peptide aggregated during storage to form an inactive species. Therefore, we developed analogs of this peptide designed to prevent aggregation and enhance the structural stability. Here, we report two analogs that retain biological activity during prolonged storage. EMTOVNOG, where O is 4-hydroxproline, is a linear peptide that was generated by substituting two prolines with 4-hydroxyproline. These substitutions were expected to reduce the aggregation potential of the peptide by increasing its hydrophilicity. This peptide exhibited a dose-dependent growth inhibition of immature mouse uterus similar to that of EMTPVNPG with the maximum activity at 1 ug/mouse. A second analog cyclo-(EMTOVNOGQ) was a hydrophilic, cyclic peptide analog. In addition to reduced aggregation potential of the peptide, this cyclic analog was expected to have increased structural stability that might be useful for future NMR studies intended to lead to a peptido mimetic. Cyclized peptide was as potent as the other peptides in its inhibition of estrogen-dependent growth of immature mouse uterus. Both analogs exhibited indefinite shelf life, which is a significant improvement over EMTPVNPG. Further, both analogs inhibited the estrogen-dependent growth of MCF7 human breast cancer growing as xenografts in SCID mice. These analogs, which are derived from a safe, non-toxic, naturally occurring human protein, may become significant, novel agents for the treatment, prevention, and perhaps even detection of breast cancer.

This work was supported by Training Grant DAMD 17-99-1-9054 from U.S. Army and EMPIRE Grant ANDT01 from New York State Department of Health.



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